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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/082,804	02/22/2002	Lisa C. McConlogue	MBHB02-329-A	2073

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/082,804	MCCONLOGUE ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,6,9,13-28,30-39 and 42-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,9,13-28,30-39 and 42-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 27, 2005 has been entered.

Claims 1, 2, 5, 6, 9, 13-28, 30-39 and 42-55 are pending.

Applicant's amendment has overcome the rejection made in the office action mailed January 25, 2005 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5, 6, 9, 13-28, 30-39 and 42-55 remain rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility for reasons set forth in the rejection mailed June 28, 2004 and January 25, 2005.

Claims 1, 2, 5, 6, 9, 13-28, 30-39 and 42-55 lack either a specific or substantial utility.

Applicant argues that the invention has a specific utility because transgenic BACE knockout animals comprising at least one nonfunctional allele of a BACE-1 gene are unique tolls

for he further study of Alzheimer's disease and for the development of therapeutics to treat AD. Applicant argues that the claimed transgenic mice and methods of using the mice have a specific utility in the screening for inhibitors of β-secretase activity, inhibitors of other proteases and assay for the side effects of the inhibitors. Applicant argues that the BACE-1 knockout mice can be used to screen for a specific inhibitor of the production of a specific peptide, such as one associated with Alzheimer's disease, and thus identify a compound for the treatment of Alzheimer's disease. Applicant argues that the MPEP states that an invention has to have a clear, specific and unquestionable utility, and the present invention has such. Applicant argues their invention, unlike chromosome markers or a gene probe that doesn't specific a DNA target, is specific for a non-BACE-1 protease that causes the production of an Aβ peptide. Applicant argues that such non-BACE-1 proteases may include γ-secretase, presenilin-1, pesenillin-2 and BACE-2. Applicant argues that their transgenic animal is uniquely suited for determining side effects of a BACE inhibitor. These arguments are not persuasive.

Any animal can be used to for any of the utilities argued by applicant. If the animal is a homozygous knockout for BACE-1, then it certainly can't be used to assay for BACE-1 inhibitors. Further, any mouse, or animal, can be used to determine the side effects of a BACE-1 inhibitor. In addition, any mouse, or animal, can be used to screen for an inhibitor of the production of a specific peptide, recognized by an antibody that recognizes residues 13-28 of Aβ, whether the inhibitor recognizes γ-secretase, presenilin-1, presenilin-2 or BACE-2, or to determine side effects of a BACE-1 inhibitor. The claimed BACE-1 mice are not specific for determining an inhibitor to treat Alzheimer's disease, or determining side effects of a BACE-1 inhibitor. In this context, any mouse, wild type or any one of the myriad of mice overexpressing an APP DNA sequence encoding a familial AD mutation can be used to screen for inhibitors of BACE-1, again,

regardless of inhibitor target. These mice can also be used to determine side effects of BACE-1 inhibition. MPEP 2107.01 states:

> A "specific utility" is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention.

The presently claimed mice, cells and methods as assays for inhibitors of A/B production, or determining side effects of BACE-1 inhibitors is not a utility specific for the presently claimed mice, but a general utility for a broad category of mice, cells and assays. For example, mice expressing an APP-FAD DNA sequence, specifically related to formation of A/β deposits in Alzheimer's disease patient's brain. The presently claimed mice, cells and assay are not so related. They do not have any feature to them that predisposes them to develop Alzheimer's disease symptoms or features. In fact the absence of BACE-1 makes them less likely to develop any hallmark features of Alzheimer's disease, as demonstrated in the specification. This lack of a specific utility is substantiated by the specification and is based on the disclosure.

Applicant argues that the claimed invention has a substantial utility because the BACE-1 knockout mice and screening assay can be used to screen for an inhibitor of A/β production. Applicant argues that this is a real world utility. Applicant argues that determining BACE-1 inhibitor side effects also has a real world use s the inhibitor has a real world use in the treatment of Alzheimer's disease. These arguments are not persuasive.

The claims lack substantial utility because further research would be required to determine a role of other proteases in Alzheimer's disease and A/β formation. The γ-secretase cleavage is not known to be a due to a specific enzyme, "γ-secretase," but might be due to a single enzyme with less that perfect specificity or carboxypeptidase activity (Hardy, page 154, col. 2, parag. 1, lines 23-28). Further, wild type presenilin isn't associated with Alzheimer's

disease. BACE-2 generated fragments have not been found in senile plaques associated with Alzheimer's disease and, in tissue culture studies, are less neurotoxic than A/β generated by BACE-1 (Farzan, page 9716, col. 2, parag. 2, lines 13-17). Thus, the specifically indicated "other proteases" of γ-secretase, BACE-2, presenilin-1 and presenilin-2, do not have a substantial utility. For other proteases, further research would be required to determine if there were any other proteases involved in A/β formation and Alzheimer's disease prior to determining inhibitors of these proteases. Since further research would need to be performed to determine if the claimed mice, cells and assay methods are representative of Alzheimer's disease, there is no substantial utility for determining any side effects from protease inhibitors. There is no substantial utility until is established that proteases other than BACE-1 are involved in Alzheimer's disease.

Claims 1, 2, 5, 6, 9, 13-28, 30-39 and 42-55 remain also rejected under 35 U.S.C. § 112, first paragraph for reasons set forth in the rejection mailed June 28, 2004 and January 25, 2005. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1, 2, 5, 6, 9, 13-28, 30-39 and 42-55 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification states that the mice, methods and cells are for the identification of inhibitors of β-secretase and other proteases involved in A/β formation. However, as indicated

above in the utility rejection, the art at the time of filing did not teach that "other proteases" were involved in A/β formation or involved in the onset of Alzheimer's disease. The γ-secretase cleavage is not known to be a due to a specific enzyme, "γ-secretase," but might be due to a single enzyme with less that perfect specificity or carboxypeptidase activity (Hardy, page 154, col. 2, parag. 1, lines 23-28). Further, wild type presenilin isn't associated with Alzheimer's disease. BACE-2 generated fragments have not been found in senile plaques associated with Alzheimer's disease and, in tissue culture studies, are less neurotoxic than A/β generated by BACE-1 (Farzan, page 9716, col. 2, parag. 2, lines 13-17). Thus, the claimed invention has no enabled use because the specification fails to provide guidance on how to use any of the identified inhibitors absent a treatment for Alzheimer's disease.

The claims are free of prior art.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

August 6, 2005